LIDOCAINE HYDROCHLORIDE AND DEXTROSE - lidocaine hydrochloride and dextrose hydrous injection, solution
HOSPIRA, INC.

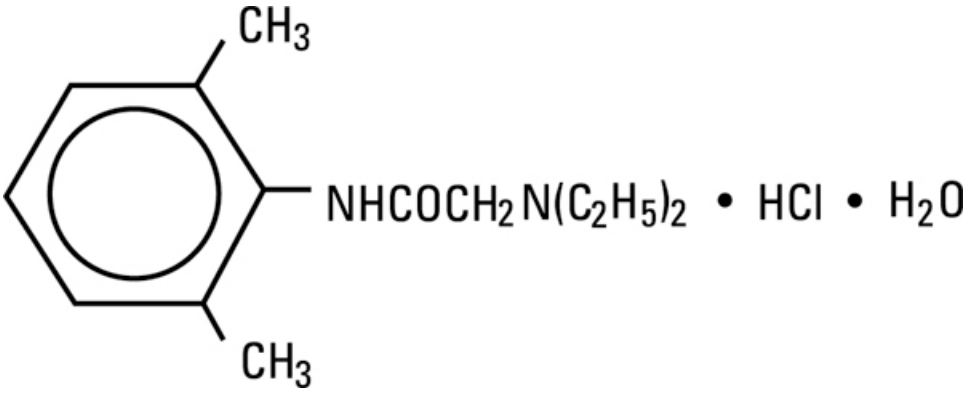
Ampul
Single-dose Container
R_x only

DESCRIPTION

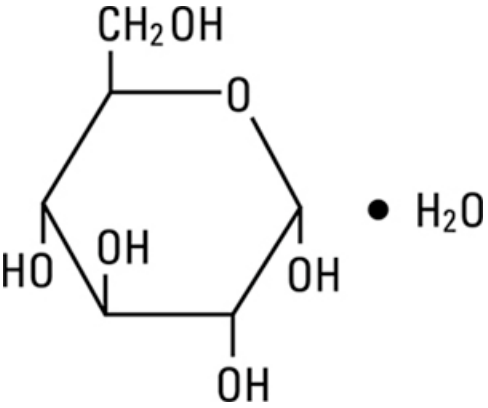
5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP is a sterile, nonpyrogenic, hyperbaric solution for use in spinal anesthesia.

5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP contains lidocaine HCl, which is chemically designated as 2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide monohydrochloride, monohydrate and Dextrose (D-Glucose monohydrate) which have the following structural formulas:

Lidocaine Hydrochloride (monohydrate)



Dextrose (hydrous)



5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP contains 50 mg/mL of lidocaine hydrochloride, anhydrous with 75 mg/mL of dextrose, hydrous in water for injection. May contain sodium hydroxide and/or hydrochloric acid for pH adjustment. pH 6.5 (6.0 to 7.0). The osmolar concentration is 0.75 mOsmol/mL (calc.). The specific gravity is 1.030 to 1.035.

CLINICAL PHARMACOLOGY

Mechanism of action: Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

Onset and duration of anesthesia: The onset of action is rapid. The duration of perineal anesthesia provided by 1 mL (50 mg) 5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP averages 100 minutes, with analgesia continuing for an additional 40 minutes. The duration of surgical anesthesia provided by 1.5 to 2 mL (75 to 100 mg) of this agent is approximately two hours.

Hemodynamics: Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to block of autonomic fibers, or a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

Pharmacokinetics and metabolism: Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 mcg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.
Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.
Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/ toxicologial actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline.
The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.
Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per mL. In the rhesus monkey arterial blood levels of 18 to 21 mcg/mL have been shown to be threshold for convulsive activity.

INDICATIONS AND USAGE
5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP is indicated for the production of spinal anesthesia when the accepted procedures for this technique as described in standard textbooks are observed.

CONTRAINDICATIONS
Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type.
The following conditions preclude the use of spinal anesthesia:
1. Severe hemorrhage, shock or heart block

2. Local infection at the site of proposed puncture

3. Septicemia

4. Known sensitivity to the local anesthetic agent.

WARNINGS
5% LIDOCAINE HYDROCHLORIDE AND 7.5% DEXTROSE INJECTION, USP FOR SPINAL ANESTHESIA SHOULD BE EMPLOYED ONLY BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES THAT MIGHT ARISE FROM SPINAL ANESTHESIA AND THEN ONLY AFTER ENSURING THE IMMEDIATE AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY EQUIPMENT, AND THE PERSONNEL NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES (See also ADVERSE REACTIONS and PRECAUTIONS). DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.
To avoid intravascular injection, aspiration should be performed before the local anesthetic solution is injected. The needle must be repositioned until no return of blood can be elicited by aspiration. Note, however, that the absence of blood in the syringe does not guarantee that intravascular injection has been avoided.
Spinal anesthetics should not be injected during uterine contractions since spinal fluid current may carry the drug farther cephalad than desired.

PRECAUTIONS

General:
The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for spinal anesthetic procedures. Resuscitative equipment, oxygen and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the physical condition of the patient. Debilitated, elderly patients, acutely ill patients and children should be given reduced doses commensurate with their age and physical status. Lidocaine should also be used with caution in patients with severe shock or heart block.

Neurologic deficits have been reported with the use of small bore needles and microcatheters for spinal anesthesia. It has been postulated, based on *in vitro* models, that these deficits were due to pooling and non-uniform distribution of concentrated local anesthesia within the subarachnoid space.[1] Animal studies suggest mixing of 5% lidocaine hydrochloride with an equal volume of CSF or preservative-free 0.9% saline solution may reduce the risk of nerve injury due to pooling of concentrated local anesthetic.[2] (See DOSAGE AND ADMINISTRATION.).

The following conditions may preclude the use of spinal anesthesia, depending upon the physician's ability to deal with the complications or complaints that may occur:

a. Pre-existing diseases of the central nervous system such as those attributable to poliomyelitis, pernicious anemia, paralysis from nerve injuries, and syphilis.

b. Disturbance in blood morphology and/or anticoagulant therapy. In these conditions, trauma to a blood vessel during needle puncture may result in uncontrollable hemorrhage into the epidural or subarachnoid space. Also profuse hemorrhage into the soft tissue may occur.

c. Extremes of age.

d. Chronic backache and preoperative headache.

e. Hypotension and hypertension.

f. Arthritis or spinal deformity.

g. Technical problems (persistent paresthesias, persistent bloody tap).

h. Psychotic or uncooperative patients.

CONSULT STANDARD TEXTBOOKS FOR SPECIFIC TECHNIQUES AND PRECAUTIONS FOR SPINAL ANESTHETIC PROCEDURES.

Careful and constant monitoring of cardiovascular and respiratory (adequacy of ventilation) vital signs and the patient's state of consciousness should be accomplished after each local anesthetic injection. It should be kept in mind at such times that restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Since amide-type local anesthetics are metabolized by the liver, lidocaine should be used with caution in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetic normally, are a greater risk of developing toxic plasma concentrations. Lidocaine should also be used with caution inpatients with impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. Since it is not known whether amide-type local anesthetics may trigger this reaction and since the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment including oxygen therapy, indicated supportive measures and dantrolene (consult dantrolene sodium intravenous package insert before using).

Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

Information for Patients:

When appropriate, patients should be informed in advance that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia.

Clinically significant drug interactions:

The administration of local anesthetic solutions containing epinephrine or norepinephrine to patients receiving monoamine oxidase inhibitors, tricyclic antidepressants or phenothiazines may produce severe, prolonged hypotension or hypertension. Concurrent use of these agents should generally be avoided. In situations when concurrent therapy is necessary, careful patient monitoring is essential. Concurrent administration of vasopressor drugs (for the treatment of hypotension related to spinal blocks) and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accidents.

Carcinogenesis, mutagenesis, impairment of fertility:

Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Use in Pregnancy: *Teratogenic Effects. Pregnancy Category B.*

Reproduction studies have been performed in rats at doses up to 6.6 times the human dose and have revealed no evidence of harm to the fetus caused by lidocaine. There are, however, no adequate and well-controlled studies in pregnant women. Animal reproduction studies are not always predictive of human response. General consideration should be given to this fact before administering lidocaine to women of childbearing potential, especially during early pregnancy when maximum organogenesis takes place.

Labor and delivery:
Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate also should be monitored continuously, and electronic fetal monitoring is highly advisable.
Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. However, spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. The use of obstetrical anesthesia may increase the need for forceps assistance.

Nursing mothers:
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when lidocaine is administered to a nursing woman.

Pediatric use:
Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

ADVERSE REACTIONS
Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported:
Central nervous system: CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, lethargy, slurred speech, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.
Drowsiness following the administration of lidocaine is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.
Cardiovascular system: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.
Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions as a result of sensitivity to lidocaine are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.
Neurologic: The incidences of adverse reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and are also dependent upon the particular drug used, the route of administration and the physical status of the patient. In a prospective review of 10,440 patients who received lidocaine for spinal anesthesia, the incidences of adverse reactions were reported to be about 3 percent each for positional headaches, hypotension and backache; 2 percent for shivering; and less than 1 percent each for peripheral nerve symptoms, nausea, respiratory inadequacy and double vision. Many of these observations may be related to local anesthetic techniques, with or without a contribution from the local anesthetic.
Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities, and loss of sphincter control all of which may have slow, incomplete, or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningismus, arachnoiditis; slowing of labor; increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; and fecal and urinary incontinence.

OVERDOSAGE
Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use of local anesthetics or to unintended subarachnoid injection of local anesthetic solution (see ADVERSE REACTIONS, WARNINGS, and PRECAUTIONS).
Management of local anesthetic emergencies: The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. At the first sign of change, oxygen should be administered.
The first step in the management of convulsions, as well as underventilation or apnea due to excessive cephalad spread of the spinal block, consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. Immediately after the institution of these ventilatory measures, the adequacy of the circulation should be evaluated, keeping in mind that drugs used to treat convulsions sometimes depress the circulation when administered intravenously. Should convulsions persist despite adequate respiratory support, and if the status of the circulation permits, small increments of an ultra-short acting barbiturate (such as thiopental or thiamylal) or a benzodiazepine (such as diazepam) may be administered intravenously. The clinician should be familiar, prior to use of local

anesthetics, with these anticonvulsant drugs. Supportive treatment of circulatory depression may require administration of intravenous fluids and, when appropriate, a vasopressor as directed by the clinical situation (e.g., ephedrine).
If not treated immediately, both convulsions and cardiovascular depression can result in hypoxia, acidosis, bradycardia, arrhythmias and cardiac arrest. Underventilation or apnea due to excessive cephalad spread of the spinal block may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest should occur, standard cardiopulmonary resuscitative measures should be instituted.
Endotracheal intubation, employing drugs and techniques familiar to the clinician, may be indicated, after initial administration of oxygen by mask, if difficulty is encountered in the maintenance of a patent airway or if prolonged ventilatory support (assisted or controlled) is indicated.
Dialysis is of negligible value in the treatment of acute overdosage with lidocaine.
The intravenous LD_{50} of lidocaine HCl in female mice is 26 (21 to 31) mg/kg and subcutaneous LD_{50} is 264 (203 to 304) mg/kg.

DOSAGE AND ADMINISTRATION

Spinal anesthesia with 5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP may be induced in the right or left lateral recumbent or the sitting position. Since this is a hyperbaric solution, the anesthetic will tend to move in the direction in which the table is tilted. After the desired level of anesthesia is obtained and the anesthetic has become fixed, usually in 5 to 10 minutes with lidocaine, the patient may be positioned according to the requirement of the surgeon or obstetrician.
In clinical trials, the safety of hyperbaric lidocaine for single injection spinal anesthesia was demonstrated using 22 or 25 gauge spinal needles. In these studies, free flow of CSF was visible before injection of lidocaine.
Neurologic deficits have been reported with the use of small bore needles and microcatheters for spinal anesthesia. It has been postulated, based on *in vitro* models, that these deficits were caused by pooling and non-uniform distribution of concentrated local anesthetic within the subarachnoid space.[1] Animal studies suggest mixing of 5% lidocaine hydrochloride with an equal volume of CSF or preservative-free 0.9% saline solution may reduce the risk of nerve injury due to pooling of concentrated local anesthetic.[2] (See PRECAUTIONS).
Intrathecal distribution of anesthetic may be facilitated by using a spinal needle of sufficient gauge to insure adequate withdrawal of CSF through the needle prior to and after anesthetic administration. If the technique is properly placed in the subarachnoid space, a separate injection is seldom necessary.
An incomplete or patchy block not responsive to patient repositioning may indicate misplacement or inadequate distribution of drug. To avoid excessive drug pooling, additional doses of lidocaine should not be administered with the same needle placement.
INJECTIONS SHOULD BE MADE SLOWLY. Consult standard textbooks for specific techniques for spinal anesthetic procedures.

Recommended dosages

Normal healthy adults: The following recommended dosages are for normal healthy adults and serve only as a guide to the amount of anesthetic required for most routine procedures. In all cases, the smallest dose that will produce the desired result should be given. If the technique is properly performed, and the needle is properly placed in the subarachnoid space, it should not be necessary to administer more than one ampul (100 mg).

Obstetrical low spinal or "saddle block" anesthesia:

The dosage recommended for normal vaginal delivery is approximately 1 mL (50 mg). For Caesarean section and those deliveries requiring intrauterine manipulations, 1.5 mL (75 mg) is usually adequate.

Surgical anesthesia:

The dosage recommended for abdominal anesthesia is 1.5 to 2 mL (75 to 100 mg).

Pediatric Patients:

The dosage recommendations in healthy adolescents, 16 years of age and older, is the same as for normal healthy adults. There is insufficient data in pediatric patients below the age of 16 years to make dosage recommendations (see PRECAUTIONS).
NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever the solution and container permit. Solutions that are discolored and/or contain particulate matter should not be used.
Unused portions of solutions should be discarded following initial use.
5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP may be autoclaved once at 15 pounds pressure, 121°C (250°F) for 15 minutes. Since this preparation contains dextrose, carmelization may occur under prolonged heating and, in some instances, prolonged storage. Therefore this preparation should not be autoclaved more than once, according to the above instructions, and should not be permitted to remain in the autoclave any longer than necessary. Do not administer any solution which is discolored or contains particulate matter.

HOW SUPPLIED

5% Lidocaine Hydrochloride and 7.5% Dextrose Injection, USP is supplied in a single-dose 2 mL ampul (List No. 4712).
Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]

1. Lambert DH and Hurley RJ: Cauda Equina syndrome and continuous spinal anesthesia. Anesth and Analg 72:817-9, 1991.

2. Ready, LB, et al: Neurotoxicity of local anesthetics in rabbits. Anesthesiology 63:364-70, 1985.

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